Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

A science and risk-based approach to product quality regulation incorporating an integrated quality systems approach

Introduction

FDA oversees the quality of drug products* using a two-pronged approach involving review of information submitted in applications as well as inspection of manufacturing facilities for conformance to requirements for current Good Manufacturing Practice (cGMP). These two programs have served the country well by helping to ensure the quality of drug products available in the US. Now, as we approach the 25th anniversary of the last major revision to the drug cGMP regulations, it is time to step back and evaluate the currency of these programs so that:

- the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality;
- the latest scientific advances in pharmaceutical manufacturing and technology are encouraged;
- the submission review program and the inspection program operate in a coordinated and synergistic manner;
- regulation and manufacturing standards are applied consistently;
- management of the program encourages innovation in the pharmaceutical manufacturing sector; and
- FDA resources are used most effectively and efficiently to address the most significant health risks.

To these ends, FDA is undertaking an initiative, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach."

Merging Science-Based Risk Management with an Integrated Quality Systems Approach

Over the last two decades, significant changes in the environment of pharmaceutical regulation have occurred and have resulted in incremental adjustments in FDA's regulatory approach to product quality. These changes include:

- Increased number of pharmaceutical products and a greater role of medicines in health care
- Decreased frequency of FDA manufacturing inspections as a result of fewer resources available for pharmaceutical manufacturing inspections
- FDA's accumulation of experience with, and lessons learned from, various approaches to the regulation of product quality
- Advances in the pharmaceutical sciences and manufacturing technologies
- Application of biotechnology in drug discovery and manufacturing
- Advances in the science and management of quality
- Globalization of the pharmaceutical industry

* As used in the this paper, the terms "drug" and "pharmaceutical" include veterinary drugs and human drugs, including human biological drug products. The terms are not intended to extend to veterinary Type A medicated articles or veterinary medicated feed products.

The cumulative impact of these changes has been greater than the sum of the parts, and warrants a systematic reappraisal of FDA's approaches to product quality regulation. The following principles will guide implementation of the reappraisal:

Risk-based orientation In order to provide the most effective public health protection, FDA must match its level of effort against the magnitude of risk. Resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production. Although the agency has been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed.

Science-based policies and standards Significant advances in the pharmaceutical sciences and in manufacturing technologies have occurred over the last two decades. While this knowledge has been incorporated in an ongoing manner into FDA's approach to product quality regulation, the fundamental nature of the changes dictates a thorough evaluation of the science base to ensure that product quality regulation not only incorporates up-to-date science, but also encourages further advances in technology. Recent science can also contribute significantly to assessment of risk.

Integrated quality systems orientation Principles from various innovative approaches to manufacturing quality that have been developed in the past decade will be evaluated for applicability, and cGMP requirements and related pre-approval requirements will be evaluated according to applicable principles. In addition, interaction of the pre-market CMC review process and the application of cGMP requirements will be evaluated as an integrated system.

International cooperation The globalization of pharmaceutical manufacturing requires a global approach to regulation. FDA will collaborate with other regulatory authorities, via ICH and other venues.

Strong Public Health Protection The initiative will strengthen the public health protection achieved by FDA's regulation of drug product manufacturing and will not interfere with strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.

To accomplish the reappraisal, FDA will carry out the following broad actions:

- Perform an external review of the existing cGMP program and product review practices, including evaluation of potential inconsistencies in implementation
- Reassess and reevaluate our current scientific approach to both the product review process and the cGMP program to achieve a consistent, integrated systems approach to product quality regulation
- Enhance the scientific approach of cGMPs to emphasize risk-based control point analysis and to facilitate the latest innovations in pharmaceutical engineering

The following immediate steps are planned:

- Holding scientific workshops with key stakeholders
- Enhancing expertise in pharmaceutical technologies (e.g., pharmaceutical engineering and industrial pharmacy) by additional training and hiring, and by leveraging external expertise
- Encouraging innovation within the existing framework of statutory provisions and regulations by allowing certain changes in the manufacturing process without prior review/approval (e.g., comparability protocols)
- Evaluating the optimal mechanisms to effectively and efficiently communicate deficiencies to industry, including content, consistency, disclosure, and education
- Shifting the agency lead on implementation of Part 11 to CDER, with continued involvement from the other Centers and ORA
- Including product specialists, as needed, as a part of inspection teams.
- Having Centers provide a scientific and technical review of all drug cGMPWarning letters
- Developing a technical dispute resolution process that integrates technical experts from the Centers and addresses perceived inconsistencies between Centers
- Emphasizing a risk-based approach in the work planning process
- Improving the operations of Team Biologics

Intermediate Steps

- Use emerging science and data analysis to enhance compliance programs to target the highest risk areas
- Evaluating the feasibility of establishing dedicated cadres of pharmaceutical inspectors

Long term Steps

- Enhanced training of agency staff on new scientific approaches and innovative pharmaceutical manufacturing technology
- Develop and publish policies and procedures reflecting a science-based, risk management approach
- Educate industry on new regulatory approaches encouraging innovation

Authority

Current regulations (21 CFR Parts 210, 211, 600 and 610) appear to provide a degree of flexibility to allow the agency to shift the emphasis to a science-based, risk management approach. However, an evaluation of the comments from the May 1996 proposed drug cGMP amendments will continue and consideration will be given to revising these regulations and others (e.g., 21 CFR 11) in the future. In addition, efforts currently underway to revise existing regulations (e.g., 21 CFR 600-610) to allow for more flexibility will continue.